REMARKS

STATUS OF THE CLAIMS

Claims 8-19 and 21-30 were pending in this application. Claims 10, 21 and 22 have been cancelled without prejudice. Claims 8, 23, 27, and 30 have been amended. Following entry of the amendments claims 8, 9, 11-19 and 23-30 will be pending and at issue.

SUPPORT FOR AMENDMENTS TO THE CLAIMS

Claim 8 has been amended to include the term "wherein the T-cells are cultured in the presence of natural or synthetic myelin proteins and wherein said human is in need of treatment for multiple sclerosis." Support can be found throughout the specification as filed, e.g., page 7, lines 19-21 and page 8, lines 10-11, and original claims 10, 21, and 22.

Claims 23 and 27 and 30 have been amended to correct dependency.

To further prosecution, Applicant has cancelled without prejudice claims 10, 21 and 22 rendering the pending rejections moot. Applicant reserves the right to file subsequent applications claiming the canceled subject matter. In addition, the claim cancellations should not be construed as abandonment or agreement with the Examiner's position in the Office Action.

The amendments to the claims therefore add no new matter and entry is respectfully requested.

OBJECTIONS TO THE SPECIFICATION

The specification was objected to as allegedly failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o).

The Examiner stated that "The methods of '**Claims 8-19**, a method of mediating an immune response comprising the step of administering attenuated T cells to a human, and the limitations of Claims 9-19, have no antecedent basis in the specification. The specification discloses only the use of attenuated T cells for the treatment of autoimmune diseases and specifies only multiple sclerosis (MS)." Applicant respectfully disagrees, and points out that the specification as originally filed, e.g., parent application 09/156,509 filed 09/17/1998, included claim 8. As the claims form part of the specification, the specification included antecedent basis

for the method of claim 8. However, without agreeing with the Examiner's position but rather to expedite prosecution, Applicant has amended claim 8 to include the element of wherein said human is in need of treatment for multiple sclerosis. As noted by the Examiner, the specification discloses treatment of multiple sclerosis; withdrawal of this objection is respectfully requested.

The Examiner stated that "The method of **Claims 10, 26, and 28** wherein natural and/or synthetic myelin proteins are employed, have no antecedent basis in the specification." Applicant respectfully disagrees, and points out that antecedent basis for both natural and synthetic myelin proteins can found beginning at page 8, line 10: "Preferably, the PBMCs obtained are cultured in the presence of cow myelin proteins or synthetic complete human proteins as they are identified and become available." Further support for the language "natural" can be found at, e.g., beginning at page 10, line 21: " ... and stimulated with bovine total myelin proteins prepared according to standard protocols (Correale J, M McMillan, et al. (1995) Neurology 45:1370- 1378) ...." Accordingly, Applicant requests withdrawal of this objection.

REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 21-30 are rejected under 35 U.S.C. 112, second paragraph, as allegedly being incomplete for omitting essential steps, such omission amounting to a gap between the steps. The Examiner stated that "The omitted steps are: the method of Claim 21 recites no steps. The method of Claim 21 depends from canceled product Claim 1. Thus, the method of the claim, i.e., "the method of Claim 1..." comprises no method steps."

Applicant thanks the Examiner for a careful reading of the claims, and notes that Claim 21 as originally drafted included a typographical error and should have depended on claim 8 and not claim 1. However, in the instant Response, claims 21 and 22 have been cancelled, and claims 23-30 now ultimately depend on method claim 8, rendering the rejection moot; withdrawal is respectfully requested.

REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 8-21 were rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled

in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner stated that "Specifically, the specification provides insufficient evidence that the claimed method could be used for mediating an immune response other than a T cell immune response such as the response in an MS patient."

Without agreeing with the Examiner's rejection but to expedite prosecution of this application, Applicant has amended claim 8 to include "wherein said human is in need for treatment of multiple sclerosis." Withdrawal of this rejection is respectfully requested.

Claims 24, 25, and 30 were rejected under 35 U.S.C. § 112, first paragraph, as the specification allegedly does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The Examiner stated that "The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically, the recitation of:

A) The method of Claim 24 comprising at least two of MBP, MOG, PLP, and MAG.

B) The method of Claim 25 comprising at least MBP, MOG, PLP, and MAG.

C) The method comprising the specific steps set forth in Claim 30."

Applicant respectfully disagrees, and notes that various terms used in the specification, e.g., "bovine myelin proteins," "synthetic complete human myelin proteins" and "myelin antigens" describe a plurality of myelin proteins. As described in the specification, in art cited by the Examiner, and as is well known to one of skill in the art, myelin includes more than one myelin protein including but not limited to, e.g., myelin basic protein (MBP), proteolipid protein (PLP), myelin associated glycoprotein (MAG), and myelin-oligodendrocyte glycoprotein (MOG).

Support for a plurality of myelin proteins can found at, e.g., beginning at page 8, line 10 "Preferably, the PBMCs obtained are cultured in the presence of cow myelin proteins or synthetic complete human proteins as they are identified and become available;" beginning at page 10, line 21 "... PBMCs were cultured in serum free media supplemented with gentamicin and stimulated with bovine total myelin proteins ...;" and beginning at page 11, line 5 "Cycles of

restimulation and expansion were repeated weekly until the response to myelin antigens ..." Clearly the specification contains sufficient written description and reasonably conveys to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. Withdrawal of this rejection is respectfully requested.

REJECTIONS UNDER 35 U.S.C. § 102

Claims 8-12, 14 and 15 are rejected under 35 U.S.C. 102(b) as allegedly anticipated by Stinissen et al. (1996). The Examiner stated that "Stinissen et al. teaches a method of mediating an immune response comprising administering irradiation-attenuated T-cells derived from autologous peripheral mononuclear cells cultured in the presence of natural or synthetic myelin proteins (see particularly page 503, T CELL VACCINATION IN MS)."

Applicant respectfully points out that Stinissen (a review paper) describing the Zhang et al 1993 experiments and describes administering to MS patients T cells that have been cultured in the presence of and reactive with 2 synthetic peptides from a single myelin protein, e.g., MBP. Stinissen does not describe T-cells cultured in the presence of multiple myelin proteins, and does not describe T-cells cultured in the presence of natural or synthetic protein. In contrast, original claims 10 and 11 recited methods of administering to humans T cells that have been cultured in the presence of (claim 10) and are reactive with (claim 11) multiple myelin proteins, e.g., at least two myelin proteins, e.g., MBP and MOG, or e.g., a mixture of all myelin protein, e.g., bovine myelin proteins.

Accordingly, Stinissen does not teach each and every element of original claims 10 and 11. Applicant has herein amended claim 8 to include the element from claim 10 of wherein the T-cells are cultured in the presence of natural or synthetic myelin proteins; all remaining claims ultimately depend on claim 8 and include this element. Stinissen does not disclose the element of T-cells cultured in the presence of multiple myelin proteins or the element of natural or synthetic proteins and cannot anticipate the claims as amended. Applicant requests that this rejection be withdrawn.

REJECTIONS UNDER 35 U.S.C. § 103

Claims 16-19 were rejected under 35 U.S.C. 103(a) each as allegedly unpatentable over Stinissen et al. (1996). The Examiner stated that "Stinissen et al has been discussed above. The reference differs from the claimed invention only in that it does not teach the optimization of the claimed method as set forth in dependent Claims 16-19. For example, the choice of dosage (Claim 17), and timing (Claim 16), would have fallen well within the purview of the skilled artisan at the time of the invention. Regarding the increasing of the dosages as set forth in Claims 18 and 19, one of ordinary skill in the art at the time the invention was made would have been well aware of the concept of increasing dosage if no response is obtained up to the point of efficacy or adverse reaction. These limitations do not render the claimed method patentably distinct."

Applicant respectfully disagrees. Three requirements must be met for a prima facie case of obviousness. First, the prior art references must teach all the limitations of the claims. Second, there must be a motivation to modify the reference or combine the teachings to produce the claimed invention. Third, a reasonable expectation of success is required.

The cited prior art references do not teach all of the elements of the claims. As discussed above, the claims as amended all include the element of wherein the T-cells are cultured in the presence of natural or synthetic myelin proteins, e.g., T-cells that are cultured in the presence of multiple myelin proteins. This element is not taught or suggested by Stinissen, describing vaccination using T-cells cultured in the presence of a single myelin protein, MBP. Accordingly this rejection should be withdrawn.

Claim 13 was rejected under 35 U.S.C. 103(a) each as allegedly unpatentable over Stinissen et al. (1996) in view of Correale et al (1995). The Examiner stated that:

> Stinissen et al. has been discussed above. The reference further teaches that MBP is not the only autoantigen candidate in MS. The reference teaches that additional antigens, including PLP, MAG, and MOG might also be the targets of autoreactive T cells (see particularly page 501, column 1, second full paragraph).
>
> The reference differs from the claimed invention only in that it does not teach the use of attenuated T cells that target more than one myelin protein.

> Correale et al. extends the teachings of Stinissen et al. regarding additional MS autoantigens. The reference teaches that as MS develops, myelin breakdown exposes additional myelin antigens (besides MBP) to autoreactive T cells, thus, broadening the autoimmune response (see particularly page 1375, last paragraph - page 1376, first paragraph.)

Applicant respectfully disagrees. Three requirements must be met for a prima facie case of obviousness. First, the prior art references must teach all the limitations of the claims. Second, there must be a motivation to modify the reference or combine the teachings to produce the claimed invention. Third, a reasonable expectation of success is required. Applicant respectfully submits that none of these requirements are met by the combination of cited art. In addition, assuming arguendo that the prima facie case has been made, Applicant submits that secondary evidence rebuts the rejection.

In the following argument, Applicant cites declarations that have been submitted in the parent application serial number 09/156,509, filed 09/17/1998.

The cited prior art references do not teach all of the elements of the claims.

Stinissen, citing Zhang (1993, Science) teaches use of attenuated T cells comprising polyclonal T-cells reactive to a single myelin protein, MBP. As the Examiner has stated, Stinissen is missing the element of use of attenuated T cells comprising polyclonal T-cells reactive to more than one myelin protein.

However, Correale does not teach this element. Correale merely teaches, as the Examiner states that T cells responsive to multiple myelin proteins including MBP, PLP, MAG, and MOG can be found in MS patients. That is, Correale teaches a fact that is thoroughly discussed in Applicant's own patent application: "Presently, myelin proteins thought to be the target of an immune response in MS include ...MBP...PLP...MAG, and ... MOG." See, e.g., Specification at page 2. Applicant respectfully points out that Correale does not teach use of attenuated T cells comprising T-cells responsive to non-MBP myelin proteins. In addition, Correale does not teach methods for making a T-cell vaccine for MS, e.g., culturing T-cells in the presence of either single (non MBP) or multiple myelin proteins. Nor does Correale teach isolated T-cells responsive to either single (non MBP) or multiple myelin proteins. Accordingly, the combination of Stinissen and Correale does not include all elements of the claimed invention,

e.g., a vaccine having polyclonal T-cells reactive to multiple myelin proteins.

The cited art does not teach or provide a motivation to combine the teachings. Even if the cited art did teach all elements of the claims, and Applicant does not concede that it does, the Examiner does not and cannot point to any place in the cited art that teaches or suggests one of skill in the art to combine the references. The Examiner has failed to identify in the cited art a motivation, suggestion, or teaching of the desirability of the specific combination that was made by Applicant and claimed herein. There is nothing in Stinissen that suggests starting with the disclosed therein use of attenuated T cells comprising T-cells to MBP and combining with use of attenuated T cells comprising T-cells reactive to any other myelin proteins (an element that is not taught in Correale); there is nothing in Correale that suggests combining its teaching of multiple myelin proteins' involvement in MS with use of attenuated T cells comprising polyclonal T-cells reactive to MBP.

Applicant respectfully reminds the Examiner that a teaching, suggestion, or motivation to combine references must be to the specific combination claimed, as stated by the Federal Circuit in In re Werner Kotzab, 217 F.3d 1365 (2000):

> Most if not all inventions arise from a combination of old elements. *See* In re Rouffet, 149 F.3d 1350, 1357 (Fed Cir. 1998). Thus, every element of a claimed invention may be found in the prior art. *See id.* However, identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. See id. Rather, to establish obviousness based on a combination of the elements disclosed in the prior art, there must some motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant See In re Dance, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed Cir 1998).

In the instant case, the Examiner has not provided a teaching, suggestion or motivation to combine references must be to the specific combination claimed, e.g., use of attenuated T cells cultured in the presence of multiple myelin proteins. Instead, the Examiner states that "One of ordinary skill in the art at the time the invention was made would have been motivated to employ attenuated T cells autoreactive to multiple myelin antigens given the teachings of Stinissen et al. that MBP is not the only autoantigen candidate in MS and extended by Correale et al. that as MS

develops, myelin breakdown exposes additional myelin antigens (besides MBP) to autoreactive T cells, thus broadening the autoimmune response."

Applicant disagrees. At most, the combination of cited art provides a motivation to one of skill in the art to use attenuated T cells comprising T-cells cultured in the presence of a single, non-MBP, myelin protein. The combination of cited art does not provide a motivation to explore use of attenuated T cells comprising T cells reactive to multiple myelin proteins.

One of skill in the art would have had no expectation of success. Again assuming *arguendo* that the combination of art cited does contain all the claim elements, one of skill in the art would have had no expectation of success when combining the elements. That is, one of skill in the art would not have expected to produce a successful therapeutic use of attenuated T cells comprising polyclonal T-cells reactive to multiple myelin proteins.

Applicant has shown that the claimed invention, a vaccine having polyclonal T-cells reactive to multiple myelin proteins, is effective in treatment of secondary progressive MS. In the parent application, Applicant has submitted multiple declarations to support the arguments that this result was surprising and unexpected, e.g., that, before Applicant's invention, one of skill in the art would have had no expectation of success when using Applicant's vaccine to treat MS.

Even if prima facie obviousness could be established here, secondary evidence would rebut any such finding. In addition, secondary evidence of unexpected results, solution of a long-felt but unsolved need, failure of others, and skepticism of experts militates against a finding of obviousness here. *See, e.g., In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992); *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538, 218 U.S.P.Q. 871, 879 (Fed. Cir. 1983) ; *see also* MPEP § 716.01(a).

Applicant's invention produced unexpected results. Evidence of unobvious or unexpected advantageous properties, rebuts *prima facie* obviousness. MPEP § 716.02(a); *Ex parte A*, 17 U.S.P.Q.2d 1716, 1719 (Bd. Pat. App. & Inter. 1990) The use of attenuated T cells activated with a single myelin protein, MBP as described in Stinissen failed to produce significant clinical benefits. *See, e.g.*, Zhang (1993, Hum Immun) at 91, column 2 paragraph 1

(recognizing the "lack of significant clinical improvement regarding the disease score and magnetic resonance imaging of the brain lesions in the chronic, progressive patients in our vaccination study"); and Zhang et al. (1993, Science) at 1451-54.

In contrast, using a polyclonal mixture of T-cells that are "responsive to at least two myelin proteins" prior to attenuation, the claimed methods resulted in measurable decreases in the frequencies of T-cells reactive to three myelin proteins thought to be the target of an immune response in MS and concomitant stabilizing of neurological progression as measured by EDSS score, thus rectifying the lack of significant clinical benefits acknowledged in the cited references. *See* Specification at page 13, lines 8 – 23; Claims 20, 27.

Applicant's invention met a long felt but unsolved need. The recognized need for an effective MS treatment has persisted for more than a century without being satisfied. Although MS was first diagnosed more than 150 years ago, no effective cure or therapy for this chronic, often disabling autoimmune disease has yet emerged. *See* Specification at page 6, lines 11 – 13. The National Institutes of Health estimates that 1.1 million people suffer from MS, including approximately 350,000 MS patients in the United States. Yet the treatment alternatives known in the art fit one of two unsatisfactory profiles: nonspecific therapies that cause a general immune suppression by randomly killing or inhibiting immunocompetent cells, thus subjecting the patient to adverse effects and risks, or clonal T-cell vaccines that lack significant clinical benefits. *See* Zhang (1993, Hum Immun) at 91, column 2 paragraph 1.

The claimed vaccines generate a broad-based immune response against a wide range of antigen-specific T-cells that recognize a variety of different myelin proteins, thus rectifying the lack of significant clinical benefits acknowledged in the cited references. *See, e.g.*, Specification at page 13, lines 8 – 23; Ex. A at 132; *compare* Zhang (1993, Hum Immun) at 91, column 2 paragraph 1.

Applicant's claimed invention – in marked contrast to the prior art – satisfies the long-felt need for a clinically effective, non-toxic, antigen-specific approach to treating MS.

Applicant has succeeded where others of skill in the art have failed. Finally, the cited prior art references reflect the failure of others skilled in the art. The clonal vaccine method

taught by Zhang (disclosed in Stinissen) demonstrates a lack of significant improvement regarding disease score and other clinical measures. Indeed, Zhang posits that "in order to produce clinical benefits, T-cell vaccination may need to be applied at an earlier stage of the disease." Zhang et al. (*H. Immunol.* 1993) at 91, column 2 paragraph 1.

Using a vaccine comprising a polyclonal mixture of T-cells responsive to multiple myelin proteins prior to attenuation, Applicant has demonstrated clinical improvement in MS patients where Zhang has failed. The success of Applicant's invention, and the failure of others (e.g., Zhang) is supported by the Rule 1.132 declarations of Dr. Timothy Vollmer, submitted in the parent application on April 16, 2002 and August 30, 2002.

Accordingly this rejection should be withdrawn.

CONCLUSION

Withdrawal of the pending rejections and reconsideration of the claims are respectfully requested, and a notice of allowance is earnestly solicited. If the Examiner has any questions concerning this Response, the Examiner is invited to telephone Applicant's representative at (415) 875-2316.

Respectfully submitted,
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By: _____

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